

## Missed TB

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### The Case

A 38-year-old white female with no past medical history presented to the hospital with fevers, respiratory failure, and bilateral pulmonary infiltrates. She was treated empirically with broad-spectrum antibiotics, which were continued even after her initial blood and sputum cultures returned negative. Fevers persisted and she soon developed acute respiratory distress syndrome (ARDS). The treating physicians considered bronchoscopy, but felt the patient was too ill to tolerate the procedure. An HIV test was sent and was negative. On hospital day 21, her providers considered the possibility of tuberculosis, and sent sputum for acid-fast bacilli (AFB) smear and culture. The AFB smears were negative. The patient continued to deteriorate, with progressive respiratory failure, and died shortly afterward. Several days later, the AFB cultures began growing *Mycobacterium tuberculosis*.

### The Commentary

This case represents an unfortunate failure to identify tuberculosis (TB) in a young woman. Although TB is a common pathogen worldwide, it affects very few people in North America.<sup>(1)</sup> However, rates of TB are relatively high among the foreign born.

TB is a relatively infrequent cause of respiratory failure. In a population-based study in Manitoba over a 10-year period, Penner and colleagues identified only 13 patients with pulmonary TB requiring mechanical ventilation, compared with 722 cases of pulmonary TB and 37 cases of miliary TB during the same period.<sup>(2)</sup> The mortality rate of 69% was higher than the mortality for respiratory failure due to bacterial pneumonia (36%; p3) Because TB does not cause respiratory failure very often, it is an unlikely infectious cause of ARDS. In a prospective study of severe community acquired pneumonia (CAP) requiring mechanical ventilation, only 1 of 144 patients had pneumonia due to *M. tuberculosis*.<sup>(4)</sup>

The diagnosis of TB is often delayed. In one study of 429 hospitalized patients with newly diagnosed pulmonary TB <sup>(5)</sup>, 127 (30%) had not received antituberculous chemotherapy during their first week in the hospital. The risk of delayed treatment was particularly high in hospitals that rarely saw patients with the disease (ie, fewer than 3.3 cases of TB per 10,000 admissions). These delays are harmful: patients with

delayed diagnosis and therapy have higher rates of potentially preventable intensive care unit admissions and death. The difficulty of making an early diagnosis of TB is further compounded by the increasingly frequent use of respiratory quinolones as first-line therapy in community acquired pneumonia, since they may partly treat the active pulmonary TB and lead clinicians to be falsely reassured by a clinical response.(6)

Thus, the clinician is challenged by the relatively infrequent occurrence of TB as a cause of respiratory failure, along with the dire consequences of delayed or missed diagnoses. Clearly, it is critical to consider TB as a possible diagnosis in patients with infectious respiratory failure. Unfortunately, no signs or symptoms are sufficiently sensitive or specific to help guide decision-making. For example, the presence of cough for longer than 2 weeks (a "classic" symptom of TB) is only seen in half of patients with pulmonary TB.(7)

A pragmatic approach would be to suspect TB in all cases of severe community acquired pneumonia who fail to show a response to treatment within the first 48 hours. Clinicians should be especially vigilant in patients who are prescribed quinolones initially, and those from groups at high risk of TB. Such groups include immigrants from high prevalence TB countries, persons known to be infected with or at risk of HIV infection, or persons with a documented history of contact with an active case of TB or a positive TB skin test.

More broadly, clinicians need to recognize that "pneumonia" that does not respond to empiric antibiotic therapy has a differential diagnosis, which includes other infections, resistant organisms, as well as non-infectious conditions (Table). Like TB, each of these entities is relatively rare; however, as a group, they occur commonly enough that clinicians need to have a structured approach to evaluating "non-resolving pneumonia." In this case, the error was not so much that the clinicians failed to consider TB until hospital day 21, but that they did not consider any alternative diagnoses or complications that might explain the patient's non-resolving pneumonia in a timely fashion.

### Testing

It is important to understand that only 50% of persons will have positive sputum smears for AFB. Thus, patients who don't respond to regular antibiotics and have a radiographic pattern suggestive of TB should receive empiric treatment for TB. Induced sputum has a greater yield than bronchoscopy; it should be considered in patients who cannot provide a sputum sample.(8,9,10) In patients who do not respond to broad-spectrum antibiotics, an additional consideration is the use of CT scan imaging, which may show radiological features such as cavitation, apical nodular disease, or a "tree and bud" pattern, which may not be apparent on a plain radiograph.(11,12) Newer nucleic acid amplification based diagnostic tests have a similar yield as culture from bronchial secretions and should be considered in all patients with severe CAP who fail to respond to therapy.(11)

### Take-Home Points

- "Non-resolving pneumonia" has a broad differential diagnosis of infectious and non-infectious etiologies that clinicians need to address in a systematic and timely manner.

- Since the prognosis for missed TB in a patient presenting with severe CAP or respiratory failure is poor, TB is particularly important to consider in the approach to patients who do not respond to initial antibiotic therapy for presumed pneumonia. Most cases of missed TB can be traced to the fact that clinicians failed to consider the possibility rather than difficulties with diagnostic testing.
- Because a delay in diagnosis is associated with higher mortality, a high index of suspicion is needed. If there is any suspicion, early initiation of empiric (multidrug) anti-TB treatment is warranted. There should be a low threshold to initiate such treatment in patients who fail to respond to broad-spectrum antibiotics.
- Induced sputum or bronchial secretions should be submitted as soon as there is any clinical suspicion. Computerized tomography of the chest and nucleic acid amplification-based diagnostics may be helpful to confirm the diagnosis.
- Once TB is entertained, respiratory isolation should continue until bronchial secretions have been screened negative for AFB and the patient is responding clinically and radiologically to antibiotic treatment (or to treatment for a plausible alternative diagnosis).

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## Table

Table. Causes to Consider When Pneumonia Does Not Respond to Several Days of Empiric Antibiotic Therapy

<b>Lung Infections Requiring More Than Just Antibiotics</b>	<b>Infections Not Covered by Initial Antibiotic Choices</b>	<b>Non-Infectious Conditions</b>
Abscess	Legionella, Mycoplasma, Chlamydia (depending on initial antibiotic choice)	Pulmonary hemorrhage
Post-obstructive pneumonia	Resistant organisms (eg, Streptococcus pneumonia with high-level beta-lactam resistance)	Malignancy
Empyema (if pneumonia is accompanied by an effusion)	Influenza	Congestive Heart Failure
	TB, fungi, Nocardia, Actinomyces	Inflammatory conditions (eg, BOOP [Bronchiolitis obliterans with organizing pneumonia], Wegner's Granulomatosis)

## Drug-induced lung injury

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